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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/706,690	11/07/2000	Hyun Chul Lee	0452-0110P	8465

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EXAMINER
BUNNER, BRIDGET E

ART UNIT	PAPER NUMBER
1647	14

DATE MAILED: 08/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/706,690	LEE ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *3-7,18-25,27 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,8-17 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-28* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 24 May 2002 (Paper No. 14) has been entered in full. Claims 26-28 are added.

This application contains claims 3-7 and 18-25 drawn to an invention nonelected without traverse in Paper No. 10 (26 December 2001). A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Newly submitted claims 27-28 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 27-28 are drawn to different species of joining peptides that were not recited in the originally filed claims.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 27-28 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 4-5, and 7-13 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objections to the specification at pg 4 of the previous Office Action (Paper No. 12, 27 February 2002) are *withdrawn* in view of the amended title and specification (Paper No. 14, 24 May 2002).

Priority

2. The objection to the declaration because it does not acknowledge the filing of any foreign application is maintained and held in abeyance until all other issues are resolved. However, Applicant is encouraged to submit a corrected declaration at Applicant's earliest convenience. It is noted to Applicant that priority to the foreign document is appropriate.

Claim Rejections - 35 USC § 112

3. Claims 1-2, 8-17, and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a single-chain insulin analog compound of formula (I) having the properties of greater insulin receptor binding activity than proinsulin and less insulin receptor binding activity than insulin: B chain- X- A chain (I) wherein: B and A chains are the human insulin chains and X is a joining peptide of from 5 to 18 amino acids and has a sequence of Gly-Gly-Gly-Pro-Gly-Lys-Arg (SEQ ID NO: 1), does not reasonably provide enablement for a single-chain insulin analog compound of formula (I) having the properties of greater insulin binding activity than proinsulin and less insulin receptor binding activity than insulin: B chain- X- A chain (I) wherein: B and A chains are the human insulin chains, respectively, or functional analogs thereof; and X is a joining peptide of from 5 to 18 amino acids. Additionally, the specification, while being enabling for polynucleotide comprising the nucleic acid sequence of SEQ ID NO: 3 that encodes the single-chain insulin analog, does not provide enablement for a polynucleotide encoding the single-chain insulin analog. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Specifically, claims 1-2 , 8-17, and 26 are directed to a single-chain insulin analog compound having the properties of greater insulin receptor binding activity than proinsulin and less insulin receptor binding activity than insulin : B chain-X-A chain and wherein B and A chains are the human insulin chains and X is a joining peptide from 5 to 18 amino acids. The claims are also directed to polynucleotide encoding the single-chain insulin analog, a recombinant vector, and a cell line transfected with the vector. Claim 26 recites that the joining peptide comprises the sequence of Gly-Gly-Gly-Pro-Gly-Lys-Arg (SEQ ID NO: 1).

Applicant's arguments (Paper No. 14, 24 May 2002), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts that the creation of a peptide between 5 and 18 amino acids would not cause the skilled artisan undue experimentation. Applicant argues that, as discussed in the specification, the exact amino acids which make up the linker are not critical, as long as the amino acids do not cause the single-chain insulin analog (SIA) to form hexamers (pg 6 of response). Applicant also contends that the articles cited by the Examiner at pg 6-7 of the previous Office Action (27 February 2002; Paper No. 12) do not address a linker peptide, which by definition does not encode a functional protein, but rather is used as a bridge structure to link two peptide chains together providing the structural conformation necessary for the SIA to take up glucose and bind the insulin receptor.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, the specification of the instant application provides no methods or working examples to indicate that any linker peptides other than the sequence of SEQ ID NO: 1 (consisting of 7 amino acids) is able to properly join the A and B chains of insulin, resulting in

the correct conformation of the single-chain insulin analog (SIA) and properties of greater insulin receptor binding activity than proinsulin and less insulin receptor binding activity than insulin. Recent studies report that linkers are more than simple covalent connectors. For example, Gokhale et al. teaches that mutagenesis of key residues in the SH2-kinase linker of Src kinases plays an important role in the protein-protein interactions that stabilize the repressed state of Src family kinases (pg 23, ¶ 4). Gokhale et al. teaches that dynamic linkers establish communication by directing the correlated movements of various domains (pg 26, ¶ 3). Although Gokhale et al. mainly discuss kinases and polyketide synthase, similar ideas could be true for linker proteins of the insulin A and B chains. The skilled artisan would not be able to predict that any linker between 5 and 18 amino acids would maintain the desired activity of the insulin A and B chains recited in the claims. One skilled in the art also would not be able to predict which linker peptides do or do not cause the SIA to form hexamers. The utilization of all possible linkers from 5 to 18 amino acids may alter the conformation of the insulin A and B chains such that the analog produced does not have the properties of greater insulin receptor binding activity than proinsulin and less insulin receptor binding activity than insulin.

Furthermore, the references cited by the examiner at pages 6-7 of the previous Office Action are directed to all possible insulin A and B chain analog variants, as well as the combination of all these analogs and all possible linkers between 5 and 18 amino acids. As discussed in the previous Office Action, while it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g.

such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. For example, undue experimentation would be required of the skilled artisan to determine that all insulin A and B chain analogs are functionally equivalent as the regular insulin A and B chains. One skilled in the art would not be able to predict that all insulin A and B chain analogs would be functional since certain positions in a protein's sequence are critical for activity. The specification also does not teach any specific insulin A and B chain analogs to make up the claimed compound, other than the normal insulin A and B chains. This is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation.

(ii) Applicant asserts that the specification does provide the skilled artisan with guidance about which linkers to choose. Applicant submits that the specification discloses that the linker has the formula U_l-Z_n-Y_m-Z_l-U_n with specific limitations. Applicant argues that the specification discloses 10 specific examples of acceptable linkers. Applicant states that given the small number of possible linkers and the large number of specific examples provided in the specification, it would not be undue experimentation for one skilled in the art to make and use a linker of between 5 to 18 amino acids.

Applicant's arguments have been fully considered but are not found to be persuasive. The specification and claim 3 (withdrawn) of the instant application recite that the peptide linker has the formula U_l-Z_n-Y_m-Z_l-U_n, wherein U is an arginine or a lysine; Z is any amino acid residue; Y is a peptide; 1 is an integer of 2-n; n is an integer of 0, 1, or 2; and m is an integer of 2

to 5. The specification also discloses specific amino acid residues that may be substituted for Z and Y (pg 2, lines 28-31). The specification teaches slightly more specific amino acid sequences that could be utilized for the linker peptide (pg 14). However, this is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The structure and function of every linker regarding involvement with the insulin A and B chains is not disclosed in a manner such that one skilled in the art could make and use them without undue experimentation. Additionally, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present invention is unpredictable and complex wherein one skilled in the art may not necessarily be able to generate the infinite number of linker derivatives recited in the specification and claims and screen the same for activity.

(iii) Applicant asserts that the specification enables a polynucleotide encoding a single-chain insulin analog. Applicant contends that the insulin A and B chains can be modified in length, sequence, etc., as exemplified by the several recombinant insulin analogs known in the art. Applicant submits 6 journal articles as evidence that it would not be undue experimentation to create variants of the A and B chains. Applicant states that an application need not include what is already known in the art. Applicant explains that since (i) it would not be undue

experimentation to create a linker peptide and (ii) A and B chain variants are known in the art, the combination of all three elements (A chain, X, B chain) is within the bounds of routine experimentation.

Applicant's arguments have been fully considered but are not found to be persuasive. Although is it known in the art how to make recombinant insulin analogs, the skilled artisan cannot predict the function of all possible analogs without undue experimentation. The claims recite any functional A and B chain insulin analogs. However, as evidenced in several of the papers cited by the Applicant, the properties of insulin are *altered* by amino acid substitutions. For example, Brems et al. (Protein Engineering 5(6): 527-533, 1992) report that removal of Pro^{B28} in a series of C-terminal truncated insulins, or amino acid replacement of Pro^{B28}, greatly reduces self-association (abstract; pg 529-520, 532). Brems et al. also teaches that replacing Lys^{B29} with Pro and varying the amino acid at B^{28} greatly disrupts self-association. Brems et al. concludes that the amino acid substitutions decreased association by disrupting the formation of dimers and that "self-association of insulin can be drastically altered by substitution of one or two key amino acids" (pg 527, abstract). Schwartz et al. indicate that the human insulin analog, [Asp^{B10}]insulin (a substitution of aspartic acid for histidine), is implicated in the genetic disorder hyperproinsulinemia. Schwartz et al. disclose that [Asp^{B10}]insulin is a superactive insulin displaying in vitro potency 4-5 times greater than that of the natural hormone (abstract; pg 6410; col 1-2). Schwartz et al. teach that the superactivity of [Asp^{B10}]insulin results from stronger binding to the insulin receptor and suggest that conformational changes in [Asp^{B10}]insulin might be implicated in it's abnormal behavior (pg 6411, col 1-2). Markussen et al. (Protein Engineering 2(2): 157-166, 1988) report that in the crystal structure of insulin a hydrogen bond

bridges the α-nitrogen of A21 with the backbone carbonyl of B23 glycine. Markussen et al. synthesize a single-chain precursor B chain (1-29)-Ala-Ala-Lys-A-chain (1-21), featuring an A21 proline. Markussen et al. observe that the single-chain precursor fails to be properly produced in yeast, indicating that the formation of the hydrogen bond is an essential step in the folding process (pg 157, abstract). Therefore in regards to the instant application, one skilled in the art cannot predict that any analogs of the A and B chains of insulin in combination with any linker peptide will have the properties of greater insulin receptor binding activity than proinsulin and less insulin receptor binding activity than insulin. Undue experimentation would be required of the skilled artisan to make all possible combinations of insulin A and B chain analogs, in combination with all possible linker peptides and screen them for activity. Additionally, there is no guidance in the specification of any polynucleotide sequence encoding a functional SIA (single insulin chain) analog other than the nucleic acid sequence of SEQ ID NO: 3, encoding SIA-I.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations of the insulin A and B chain analogs, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gary L. Kunz

BEB
Art Unit 1647
August 12, 2002